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FROM THE ALLERGY DIVISION OF THE JEWISH HOSPITAL OF BROOKLYN

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Asthma and Hay Fever

Serum Electrophoresis Patterns in the Hypersensitive State. Stroh, J. E., and Eriksen, N.: Ann. Allergy **16**: 656, 1958.

Moving boundary electrophoresis analyses were made on the sera of 42 adults and 23 children in order to compare the serum-protein patterns among the following: (1) chronic asthmatics; (2) other allergics; (3) infection-prone individuals; and (4) healthy controls.

As a group, the asthmatic patients with infection had serum-protein values which were indistinguishable from the miscellaneous nonasthmatic patients (the mean values of alpha-1 and alpha-2 globulin were increased and

the mean value of albumin was decreased). The asthmatic patients without infection differed from these only in that the mean value for alpha-1 globulin was less significantly increased. Serum-protein values for patients with increased sedimentation rates showed an increase in the mean alpha-1 and alpha-2 globulin and a decrease in the mean albumin value to a degree indistinguishable statistically from either asthmatic patients with infection or miscellaneous nonasthmatic patients. Patients with increased eosinophile counts showed patterns similar to asthmatic patients without infection.

Two out of 3 untreated acute hay fever patients showed a slight variation from the normal in 2 of the globulin fractions. Only 1 of the 3 treated hay fever patients studied showed a change in the gamma globulin value. Children with chronic asthma had values similar to normal controls, and in children with recurring infections only the mean alpha-2 globulin value was significantly increased.

Thus, it appears that no specific change can be detected by routine electrophoretic studies in the serum-protein patterns of asthmatic children or adults. The changes noted by the methods employed in this investigation did not appear to be characteristic for any of the particular pathologic conditions studied. H. F.

Use of a Tranquilizing Agent (Hydroxyzine) With Prednisolone in the Control of Allergic Disorders. Fox, J. L.: Ann. Allergy **16**: 674, 1958.

Sixty-seven patients suffering from bronchial asthma, hay fever, allergic rhinitis, or urticaria were divided into two treatment groups for a double-blind clinical study to compare the effectiveness of prednisolone when used alone and when combined with hydroxyzine. The initial dosage of the steroid was 10 to 20 mg. daily in divided doses. The initial dose of hydroxyzine was 20 to 40 mg. daily, depending upon the amount of steroid being given. An effort was made to reduce the initial dosage in all cases to an adequate minimum level. Only 6 cases in each group required treatment for longer than 3 weeks. These 12 patients were treated with the alternate medications for an additional 1 or 2 weeks.

Of the 33 patients treated with prednisolone alone, 66.7 per cent experienced good to excellent results. Of the 34 patients on combined therapy, 97.1 per cent obtained good results. In the 12 patients who alternated the medication programs, significantly better results were obtained with the steroid-tranquilizer combination than with the steroids alone. Side effects of sufficient degree to require cessation of medication occurred in 12 per cent of the prednisolone-treated patients, whereas none of the patients receiving the combined form of therapy experienced significant side reactions. H. F.

A New Effective Method of Nebulizing Bronchodilator Aerosols: Clinical and Physiological Effects. Beck, G. J.: Dis. Chest **33**: 607, 1958.

The usefulness of the gaseous phase of dichlorodifluoromethane as a means of propelling bronchodilator aerosols in the treatment of bronchial asthma was investigated. Dichlorodifluoromethane in its liquid-gas equilibrium was delivered from pocket-sized cartridges through a lateral displacement valve to a modified Vaponefrin type of nebulizer. This apparatus was designed so that a replaceable cartridge and nebulizing unit were contained within one small plastic unit. The release of dichlorodifluoromethane was effected through displacement of the cartridge by a slight pressure of the thumb. The concentration of dichlorodifluoromethane in inspired air was

3.7 per cent, up to 8.1 per cent being obtained during the early part of inspiration. Isoproterenol hydrochloride in 0.5 per cent solution, 2.25 per cent racemic epinephrine, and a mixture of 0.4 per cent isoproterenol sulfate and 2 per cent phenylephrine hydrochloride were selected as bronchodilators because of the known high degree of effectiveness of these medications in resolving bronchospasm. Ten patients with bronchial asthma and pulmonary emphysema were given five inhalations of dichlorodifluoromethane from the nebulizing unit without the addition of bronchodilator. No significant changes in vital capacity were noted, and the degree of wheezing remained unchanged. One hundred patients with bronchial asthma or pulmonary emphysema were supplied with dichlorodifluoromethane-propelled units and either 2.25 per cent racemic epinephrine or 0.5 per cent isoproterenol hydrochloride for use at home over periods of one to six months. The average number of daily single inhalations with dichlorodifluoromethane cartridges was 24. The average number of days of use of one cartridge was nine. No respiratory tract or gastrointestinal tract irritation was noted. The ethereal odor of this gas was found objectionable by three patients. Headache and dizziness were reported by two patients. Six reported tremulousness and palpitation following five inhalations of bronchodilator aerosols, but none of these symptoms was experienced if dichlorodifluoromethane was inhaled alone. Thirty-two patients described better bronchodilating effects from the gas phase type of nebulizing unit than with any other type used up to that time. The mass median diameter of the particles produced by the dichlorodifluoromethane-gas-phase-propelled nebulizer with air vent open was 1.9 microns. The weight fraction of particles having a diameter of 1 to 5 microns was 70 per cent; that fraction containing large particles of a diameter of 5 microns was only 14 per cent. About 0.012 mg. of isoproterenol was inhaled per breath. The mean increase of vital capacity over the control value was 36 per cent in bronchial asthma and 34 per cent in pulmonary emphysema for 2.25 per cent racemic epinephrine and 30 per cent in bronchial asthma and 29 per cent in pulmonary emphysema for 0.05 per cent isoproterenol hydrochloride. No significant blood pressure changes were observed 15 minutes following inhalation of these 2 drugs in either normotensive or hypertensive patients. In 20 patients with pulmonary emphysema or bronchial asthma, to whom three inhalations of 0.4 per cent isoproterenol sulfate and 2 per cent phenylephrine were given in a single treatment, the clinical results were uniformly good. In an additional group of ten patients, to whom five inhalations of this compound were administered, a more pronounced subjective and objective improvement took place. In patients to whom isoproterenol combined with phenylephrine was administered, neither sinus tachycardia nor significant blood pressure changes were found. Sinus tachycardia occurred in five patients (10 per cent) following five inhalations of isoproterenol hydrochloride and in three patients (6 per cent) following administration of 2.25 per cent racemic epinephrine. The incidence of tachycardia was not related to the presence of either hypertension or heart disease. In no instance did the heart rate exceed 130 beats per minute. Palpitation occurred in one of the patients using isoproterenol hydrochloride. E. W.

The Effect of 5-Hydroxytryptamine (Serotonin) on the Respiration of Nonasthmatic and Asthmatic Subjects. I. Michelson, A. L., Hollander, W., and Lowell, F. C.: J. Lab. & Clin. Med. **51**: 57, 1958.

Twenty-two subjects without evident pulmonary disease, ranging in age from 22 to 55 years, and eight asthmatic patients, ranging in age from 22 to

45 years, received 0.5 to 1.5 mg. of 5-hydroxytryptamine (5-HT) intravenously. In 19 of 22 nonasthmatic patients, the rapid infusion of the drug caused an increase in the rate and depth of respiration, lasting from 20 to 40 seconds. The respiratory effects were associated with numbness and tingling of the extremities, flushing of the face, a burning sensation in the throat, and an occasional crampy abdominal pain. In the remaining three nonasthmatic subjects, the response was that of sudden apnea followed by a short period of hyperpnea. The 8 asthmatic patients noted the same respiratory and systemic effects as the nonasthmatic group, except that no apnea was elicited. There was no evident wheezing or any subjective or objective evidence of increased bronchial obstruction. In an effort to discover any similarity of respiratory action between 5-HT and histamine, 0.05 mg. histamine base was given by intravenous injection to several nonasthmatic subjects. No change in respiration was noted, but there were headache, sweating, flushing of the face, and a fall in blood pressure. Each subject easily distinguished these systemic effects from those caused by 5-HT. As previously noted by others, intravenous histamine in asthmatic subjects caused severe bronchial obstruction. When an intravenous injection of 5-HT capable of producing a respiratory and systemic effect was followed by a 25 mg. intravenous injection of the antihistamine (pyrilamine maleate), there was potentiation of the respiratory and systemic effect of 5-HT. The antihistaminic drug alone produced only mild sedation and some decrease in both rate and depth of respiration. To determine whether the respiratory effects noted were of central origin or were mediated through vagal fibers, atropine in doses of 1.2 mg. was given intravenously to several normal subjects. Although somewhat altered, the respiratory effect of 5-HT was not abolished, but the systemic complaints and the subjective effects were not significantly changed. Neither hexamethonium chloride (which is known to produce a prompt lowering of the blood pressure), phentolamine (Regitine), nor chlorpromazine given intravenously was effective in preventing the respiratory response of 5-HT. The benzyl analogue of 5-HT was administered in doses of from 50 to 150 mg. intravenously to seven normal persons and seven asthmatic patients. Partial to complete inhibition of the respiratory effects of intravenously injected 5-HT occurred in each instance, and the systemic side effects were also strikingly inhibited. That bronchial obstruction was not induced by the administration of 5-HT was an unexpected finding in view of studies in guinea pigs and the occurrence of wheezing in certain patients suffering from malignant carcinoid. It was suggested that the respiratory effect of intravenously administered 5-hydroxytryptamine was mediated through action on specific receptors. E. W.

Prednisone in the Treatment of Allergic Diseases in Children. Levin, S. J., and Adler, P.: Am. J. Dis. Child. **95**: 178, 1958.

Eighty-five allergic children ranging in age from 2 to 17 years were treated with prednisone. The group consisted of 55 patients with asthma, 11 with atopic dermatitis, 5 with perennial allergic rhinitis, 13 with seasonal pollinosis, and 1 with urticaria. Treatment was begun with 10 to 20 mg. of prednisone daily in divided doses, and then the amount was decreased rapidly as the patients responded to therapy. Eighteen of the 55 asthmatics required more than 1 course of therapy, 5 patients needed 3 courses of the hormone to respond adequately, and 1 patient required continuous maintenance therapy. This type of therapy prevented the onset of status asthmaticus and the need

for frequent hospitalizations. The hormone also was most effective in relieving the acute symptoms of allergic rhinitis or generalized atopic dermatitis. When the eruption was localized and could be controlled by topical steroids and routine dermatologic measures, systemic steroids were not employed. No direct relationship was noted between the age of the patient and the dosage necessary to afford relief. Younger children required only slightly less total dosage than the older children. With short-range treatment programs, untoward reactions to the therapy were insignificant. Prednisone is recommended for relief of acute allergic states, but at no time should it be used as a substitute for proper allergic management. R. W.

Treatment of Chronic Asthma With Prednisolone. Significance of Eosinophils in the Sputum. Brown, H. M.: Lancet **2**: 1245, 1958.

Ninety asthmatic patients who had not responded to bronchodilator drugs were treated with prednisolone. Some of these patients had been started on steroids before the period of observation was begun, while the others were switched to this form of therapy. Most patients were kept on 5 mg. 3 times daily but were advised to reduce their dosage as soon as their symptoms warranted it. Many patients could be maintained on 2.5 to 7.5 mg. of prednisolone daily. Sixteen young patients who had recurrent infections which responded temporarily to antibiotics but poorly to bronchodilators and who had essentially negative sputum cultures and sensitivity tests were studied more intensively. All these patients who responded dramatically to prednisolone showed eosinophils in their sputum. Thereafter, sputum samples were employed as a means of determining the suitability of a patient for prednisolone therapy. There was a striking correlation between the number of eosinophils in the sputum and the response to prednisolone therapy. Only 1 out of 57 patients with eosinophils in the sputum failed to respond to prednisolone. Patients with few eosinophils in their sputum obtained only partial relief from the administration of the steroid. When the sputum was purulent, it was always necessary to clear up the infection with antibiotics before the patient would respond to the hormone. Three patients had more frequent bouts of purulent bronchitis while taking the steroids. It is suggested that prednisolone is most useful in the treatment of refractory asthma, especially where the sputum shows a large number of eosinophils. R. W.

Instability of Grass Pollen Extracts. Hjorth, N.: Acta allergol. **12**: 317, 1958.

Grass pollen solutions in 1 ml. and 10 ml. quantities were stored from 3 days to 5 weeks after preparation in 10 ml. rubber-capped vials. A comparison was then made of the antigenic activity of the extracts in both the filled and partially filled vials by simultaneous intracutaneous testing with 0.01 ml. and measuring the resulting wheal sizes at ten minutes. Tests were performed on the same patients with similar solutions containing 0.01 per cent Tween 80 as an additive. The activity of the extract in the partially filled vial was uniformly lower than the activity of the identical solution in the completely filled vial, resulting at times in a 90 per cent reduction in potency. This reduction was equally present, whether the vials were prepared partially filled or filled to capacity and part of their contents later withdrawn. The activity of the pollen antigen solutions containing Tween 80 was independent of the volume in the vial. Violent shaking did not abolish the difference between the activity of filled and $\frac{1}{10}$ filled vials.

When 0.1 ml. of 0.1 per cent solution of Tween 80 in phosphate buffer was added to $\frac{1}{10}$ filled vials, the antigenic activity of the extract was restored, even exceeding the activity of conventional solutions in completely filled vials. In all experiments, solutions to which Tween 80 had been added uniformly provoked a greater response than those without it. Careful control studies eliminated any histamine-like effect of Tween 80 or other effects which might alter the whealing response of the allergic skin to the specific antigen. In another experiment, two 10 ml. vials filled with a 10^{-3} solution of antigen were emptied and rinsed thoroughly three times with phosphate buffer. One vial was then filled with 10 ml. of phosphate buffer and the other with buffer containing 0.01 per cent Tween 80, and they were stored for 9 days. The Tween 80 solution yielded an average wheal of 8.3 mm., whereas the other yielded one averaging 4.3 mm. The volume effect has been considered to be due to either a combination of an adsorption and surface denaturation or some modification of either or both processes on a glass surface wetted by the liquid in a thin film. Folded protein molecules tend to spread sheetlike in such an air-liquid interface with a resultant loss in functional specificity. This process is apparently reversible, for the addition of Tween reverts the loss of antigenic activity to normal. Important practical consequences of the observed phenomena were stressed, namely, that the use of partially and completely filled vials during hyposensitization therapy leads to a great fluctuation in dosage with danger of constitutional reactions and that inconsistent results may be obtained from repeated skin tests with such solutions. M. C.

Natural History of Asthma. Pearson, R. S. B.: Acta allergol. **12**: 277, 1958.

A study was made of 625 patients with bronchial asthma who attended the clinic of two London hospitals over a period of 6 years. Asthma was considered to be primary in the vast majority of these patients and secondary to infection in less than 12 per cent. Symptoms developed before the age of 10 in 261 patients (40 per cent) and between 10 and 19 years of age in 101 patients. Severe disability was present in 175 patients (28 per cent), most of whom gave a history of status asthmaticus. The proportion of severely affected patients rose with increasing age. Those in whom allergic factors alone were present seldom were severely disabled, but it was often noticed that infection of the bronchial tract and emotion stress exerted unfavorable influences.

There were 26 deaths in this series, 19 of which occurred in status asthmaticus. There were 2 deaths from anaphylaxis (with pollen responsible for one and ACTH for the other).

Remissions occurred in 47 cases and lasted from 1 to 40 years. The largest number of remissions (23) occurred between the ages of 10 and 19 years, while a smaller number took place between the ages of 20 and 29 and 30 and 39. The sexes were equally affected, and in 17 cases the period of freedom lasted for more than ten years. Remissions most frequently occurred during adolescence and the succeeding two decades. The natural history of the disease, from this study, indicated that most cases of asthma commenced during early life when allergic factors played an important role. With advance in age, those who did not improve spontaneously frequently developed infection which produced further complications of the asthma, often increasing lung damage after 40 years of age. A fatal outcome was rare in purely allergic asthma, but death did occur in those with repeated attacks of status asthmaticus. M. C.

Miscellaneous Allergies

Immunoreactions Involving Platelets. IV. Studies on the Pathogenesis of Thrombocytopenia in Drug Purpura Using Test Doses of Quinidine in Sensitized Individuals; Their Implications in Idiopathic Thrombocytopenic Purpura. Shulman, N. R.: J. Exper. Med. **107**: 711, 1958.

Detailed studies of two patients with thrombocytopenic purpura caused by quinidine are presented. Their serum antibody levels were measured by a complement fixation test and by platelet agglutination titers. Previous in vitro tests had established optimal levels of quinidine antigen required in these reactions, and these served as a basis in the selection of clinical test doses of antigen. Quinidine was infused intravenously over a period of minutes in one case and hours in the second case. Reinfusions at intervals of several weeks were carried out in the second patient as antibody levels rose anamnestically. The platelet counts were repeated frequently during infusions and served as a guide to further dosage. Comparison of levels of reaction of the in vitro and in vivo studies revealed that platelet counts fell at a considerably lower antigen level in the intact patient than was expected from the level at which complement fixation occurred. "It was concluded that the amount of antibody which attaches to platelets when thrombocytopenia develops is insufficient to cause complement fixation or platelet agglutination." It is suggested that platelets may be somewhat altered by reaction with antibody, so that the usual methods of sequestration remove them at a higher than normal rate. The time of recovery to normal platelet levels was about 4 days, the time taken for megakaryocytes to make new platelets. Bone marrow smears in these patients were not deficient in megakaryocytes which did not appear to be damaged by the allergic reaction. Capillary fragility was unaltered, even at a site treated by the placement of a patch of saturated quinidine on the skin. A detailed concept of the pathogenesis of idiopathic thrombocytopenic purpura was presented. E. K.

Poison Ivy (Rhus) Dermatitis. An Experimental Study. Kligman, A. M.: Arch. Dermat. **77**: 149, 1958.

The subject of Rhus dermatitis is completely reviewed. All the antigens in the Rhus family were found to be phenols, catechols, or resorcinols with a 15-carbon-atom chain usually unsaturated in a position meta to one of the hydroxyl radicals. The only chemical difference in the Rhus antigens was the degree of unsaturation of the side chain which increased the antigenicity. In order to study cross reactivity, patch tests were made with various phenolic compounds on Rhus-sensitive persons. Cross reactivity could be demonstrated only with compounds containing free phenolic groups and a long side chain in the 3 position. Weak cross reactions were demonstrated by all the monohydric and dihydric phenols with a 15-carbon-atom side chain and, to a lesser degree, by dihydric phenols even without a side chain. Patch tests performed with different portions of the plant indicated that only those parts of the specimen which contained sap were capable of inducing reactions. Rhus sensitivity could be induced in all subjects by adequate exposure. Patch tests performed on persons of various races (Caucasian, Negro, Hawaiian, and Puerto Rican) failed to reveal any racial immunity; however, darkly pigmented persons were found to have a lower incidence of reactivity. By patch testing with serial dilutions, sensitivity was shown to diminish gradually in Rhus-sensitive persons as they became older. Few subjects over 60 years of age showed active Rhus sensitivity. Once Rhus sensitivity was lost, it was

very difficult to reactivate it except by extreme exposure, and this was possible only in a small percentage of subjects. Children living in an institution who had never had contact with Rhus antigens and who were fed Rhus antigen prior to contact exposure were not protected against the subsequent allergic response. Topical measures, such as soap-and-water washing, barrier creams, and detoxicants commonly employed to protect against field exposure, were found to be completely worthless. No specific topical therapy was found more efficacious for symptomatic relief than the commonly employed dermatologic measures. Antihistamines were of no value. Corticosteroids comprised the only form of systemic therapy which was found to be extremely beneficial in relieving Rhus reactions. In a few cases where Rhus dermatitis was treated by the administration of Rhus antigens, serious reactions were encountered, and the author regards this form of therapy as extremely hazardous and undesirable. Investigation of oleoresins showed that some of those available commercially were totally impotent, only one being sufficiently active to produce a skin test reaction at a 1:10,000 dilution. Materials employed for immunization therapy must be prepared from poison ivy plants which have been properly handled to ensure their potency. R. W.

Mechanism and Evolution of Sensitization. With Particular Reference to the Delayed Allergic Reaction. Ratner, B., Crawford, L. V., Feldman, R., and Krimli, A.: Ann. Allergy **16**: 662, 1958.

Studies were conducted which suggested that the delayed allergic reactions which frequently follow serum injections may be an intermediate stage of hypersensitivity and not necessarily one that is unique or clearly separated from the immediate type of reaction. One hundred three children, ranging in age from 6 months to 12 years, were tested intracutaneously with 0.1 ml. of normal horse serum or of tetanus antitoxin. The site of test was the left scapular region. Eighty-seven (84.5 per cent) showed no reactions, 8 (7.9 per cent) had immediate reactions, and 3 (2.8 per cent) had delayed reactions occurring from 1 to 48 hours after the injection. The 5 remaining patients (5.4 per cent) developed local serum sickness characterized by the appearance, within 5 to 8 days after the primary injection, of an edematous rash which persisted from 3 to 7 days. From 44 to 64 days later each of these 5 patients was retested with 0.02 ml. of horse serum or of tetanus antitoxin at the original site and at a second site in the opposite scapular region. Within 4 to 18 hours, every subject developed reactions at both sites which were indistinguishable from the delayed type of tuberculin reactions and were characterized by erythema and moderate induration. From 9 to 15 days after the demonstration of the delayed type of reaction, the same 5 patients were tested with 0.02 ml. of horse serum or of tetanus antitoxin at both scapular sites and at 2 remote sites. An immediate wheal reaction developed at each of the injected sites within 10 to 15 minutes. These reactions persisted for from 1 to 3 days. Passive transfer tests performed after the appearance of the local serum sickness reactions and the immediate reaction gave negative results.

Four months after the initial tests, 45 of the 87 originally negative reactors who were still available for study were retested with 0.02 ml. of horse serum. Of these, only 23 (51 per cent) gave immediate positive wheal reactions. Neither local serum sickness nor delayed reactions were observed in this group. The reactions of the children to bovine serum were also studied. Seventeen (10.1 per cent) of the group showed immediate reactions following

the intracutaneous injection of bovine serum, and 8 (4.9 per cent) showed delayed reactions. It appeared, therefore, that these subjects had been previously sensitized to bovine serum antigen. There was not a single instance of local serum sickness following the injection of bovine serum. These observations were interpreted to mean that the delayed or tuberculin type of reaction, rather than being unique and different from the immediate type of allergic reaction, was actually an intermediate stage in the development of the immediate type of hypersensitivity. H. F.

Anaphylaxis

Anaphylaxis in Guinea Pig: Improbability of Release of Serotonin in the Schultz-Dale Reaction. Fink, M. A., and Gardner, C. E.: Proc. Soc. Exper. Biol. & Med. **97**: 554, 1958.

Much evidence has been accumulated supporting the role of histamine in guinea pig anaphylaxis, but conflicting reports have appeared regarding the role of serotonin in this reaction. In the present study, fully grown male and female guinea pigs were sensitized with intra-abdominal injections of 1 ml. of a 10 per cent protein solution containing either whole dried egg white or bovine serum albumin. Three weeks following sensitization the animals were sacrificed, and either the ileum or the uterus was removed, washed, and suspended in Tyrode's solution. Strips of tissue, 1 to 1.5 cm. long, were attached to an ink-writing kymograph and maintained in an aerated water bath at 37 to 38° C. The normal pattern of contraction was recorded, and the sensitivity of the tissue to an optimal concentration of either egg ovalbumin (EA) or bovine serum albumin (BSA) was definitely established. Prior to exposure to specific antigen, the fresh tissue strips were routinely tested for sensitivity to serotonin and histamine. A second addition of albumin was made to test for desensitization. Six uterine and seven ileal strips from sensitized guinea pigs were utilized to determine the capacity of the serotonin antagonists—lysergic acid diethylamine (LSD) and brom-lysergic acid diethylamine (BOL)—to inhibit the Schultz-Dale reaction. Testing in the presence of several concentrations of LSD and BOL demonstrated inhibition of the action of serotonin, but in no case was the response to antigen or to histamine modified. In experiments testing for drug inhibition, the antagonistic drugs were added prior to antigen instillation. Whenever the inhibitory drug resulted in the tissue's failure to respond, the potential reactivity of the strip was determined by the addition of 1 mcg. per milliliter of acetylcholine.

In experiments previously reported the action of serotonin and antigen, but not that of histamine, could be abolished by the less specific serotonin antagonists—yohimbine, bufotenin, and gramine—in concentrations of 20 mcg. per milliliter. Using higher concentrations of these three drugs on a total of twelve sensitized ileal strips, the authors found that anaphylaxis could be partially or completely blocked but that histamine responses were similarly affected. Attempts to demonstrate the release of serotonin from sensitized guinea pig lung, uterus, or ileum in the presence of highly serotonin-sensitive mouse uterus were not successful. Moreover, persisting anaphylactic contractions after antigen exposure to histamine-poisoned guinea pig uteri were not diminished in the presence of LSD or BOL. These findings indicate that serotonin may not participate in the anaphylaxis of smooth muscle in the guinea pig. H. Stryker.

Persistence of Passively Administered Homologous and Heterologous Antibody in the Guinea Pig. Chandler, M. H., Rosenberg, L. T., and Fischel, E. E.: J. Immunol. **82**: 103, 1959.

Systemic and local anaphylaxis was passively induced in guinea pigs by known quantities of guinea pig, rabbit, and mouse anti-egg albumin sera. Antisera were obtained from rabbits immunized with alum-precipitated crystalline egg albumin and from guinea pigs and mice immunized with crystalline egg albumin and Freund's adjuvants. In the experiments with systemic anaphylaxis, guinea pigs were sensitized with an intravenous injection of 1.0 ml. of diluted rabbit or guinea pig anti-hen egg albumin serum containing either 30 or 15 mcg. AbN or mouse antibody dilutions containing 60 or 30 mcg. AbN. Normal rabbit and guinea pig sera of approximate equivalence were used as controls. The animals were challenged intravenously at various intervals after sensitization. All guinea pigs sensitized with 30 mcg. AbN of rabbit or guinea pig antisera had fatal anaphylaxis when they were challenged 3 to 7 days after sensitization. When challenged at the tenth day, three of 7 animals sensitized with rabbit antisera developed fatal anaphylaxis, whereas all animals sensitized with guinea pig antisera died. This difference in persistence of sensitivity was still pronounced on the fourteenth day when only one of four animals sensitized with heterologous antiserum died when challenged, as compared with 4 out of 6 animals that had received homologous antiserum. In the animals sensitized with homologous antiserum, passive sensitivity was still strong 3 to 4 weeks after sensitization. Sensitivity induced with 15 mcg. AbN persisted for a shorter period with both heterologous and homologous antibody. With mouse antibody, thirty animals sensitized with either 30 or 60 mcg. AbN had no fatal anaphylaxis when challenged within 5 days.

In the passive cutaneous anaphylaxis (PCA) experiments, guinea pigs were injected intracutaneously at several sites with 0.1 ml. of various antibody solutions containing 0.03 mcg. AbN or with 0.1 ml. of diluted control sera. The animals were challenged at various intervals with an intravenous injection of 6 mg. of crystallized egg albumin in 1.0 ml. of distilled water and 0.5 ml. of a 0.5 per cent solution of Evans blue dye. Ten minutes later the animals were sacrificed. Areas of dye leakage measuring 0.5 cm. or more in diameter were read as positive. Reactions were of maximum intensity in the recipients of both heterologous and homologous antisera when challenged between 6 and 24 hours after intracutaneous passive sensitization. At 48 hours and to a greater degree at 72 hours, the difference in reactivity was far greater at the sites of homologous sensitization than at the sites of heterologous sensitization. With mouse anti-egg sera, all the sites were positive at 6 hours; at 24 hours, only 2 of 8 sites reacted. The authors concluded that the persistence of passive sensitivity was directly related to the amount of antibody used to sensitize and that sensitivity induced with homologous antibody persisted longer, both locally and systemically, than that induced with an equal amount of heterologous antiserum. T. CHAO.

Pharmacology, Physiology, and Pathology

Oral Medication With Preparations for Prolonged Action. Dragstedt, C. A.: J. A. M. A. **168**: 1652, 1958.

The two major methods for delaying the disintegration and absorption of drugs are discussed. They are (1) coating of the drug with some agent, such as wax or shellac, to make it resistant to gastric digestion and (2) adsorption

of the drug on an ion-exchange resin from which it is slowly eluted. The repeat-action product is a preparation from which 2 or 3 doses of the active ingredients are released at 2 or 3 presumably predetermined time intervals. The sustained-action product purports to release a portion of the active ingredient at once and subsequent portions more or less uniformly throughout the ensuing 6 to 12 hours. It is claimed that the peaks and valleys of drug concentration in the blood and tissues are obviated by these products. There is also the convenience of the administration of the drug in one dose.

In view of the many variables which come into play when a drug is ingested (such as the length of time it stays in the stomach, the amount and nature of the secretions present in the stomach and intestines, and other absorption factors), the author is of the opinion that a preparation which delays the disintegration of the administered form does so at the expense of some loss in controlling the precision of dosage. A prolonged-type preparation is not recommended where precision of dosage is important. It should be avoided with drugs which under normal circumstances are absorbed erratically from the gastrointestinal tract. In most instances, when the total dose in the preparation is more than two or three times the usual dose, prolonged-action preparations should not be used unless there is a wide margin of safety between the toxic and therapeutic doses of the drug. M. C.

Current Status of the Treatment of Adrenal Disorders. Thorn, G. W., Nelson, D. H., and Renold, A. E.: J. A. M. A. **168**: 2130, 1958.

Iatrogenic adrenal insufficiency may occur in patients with bronchial asthma after prolonged steroid therapy, presumably due to depression of the hypothalamic-pituitary system. Withdrawal of steroid therapy in these patients may precipitate an acute adrenal crisis if adrenal function has been sufficiently depressed. Reserve adrenal function may be measured without discontinuing therapy by substituting fluorocortisone for whatever steroid is being given, administering ACTH intravenously over an 8-hour period for 3 days, and measuring the urinary 17-hydroxysteroids and 17-ketosteroids. Failure to obtain an adequate response suggests that hypoadrenalism will complicate withdrawal of steroid therapy. Unfortunately, an adequate response does not necessarily indicate that the patient's own hypothalamic-pituitary system will secrete a sufficient quantity of ACTH when steroids are discontinued. At present there is no practical way of determining this point. The intermittent use of ACTH during prolonged courses of steroids may prevent or minimize severe adrenal atrophy but will not minimize the hypothalamic or pituitary inhibition which may be the more serious problem. A new technique of administering steroids which might solve some of these problems is under investigation. It consists of alternating a high dose of steroids for one to two days with a respite of one to two days, without loss of clinical regulation. With this procedure, adrenal cortical inhibition has been observed to be significantly modified. M. C.

Ulcerogenic Properties of Steroids. Robert, A., and Nezamis, J. E.: Proc. Soc. Exper. Biol. & Med. **99**: 443, 1958.

Female rats were fasted for four days while they received cortisol or delta-cortisol. Control animals were injected with the vehicle. The concurrent administration of antibiotics to inhibit infection did not interfere with ulcer formation. Animals were killed and autopsied after four days. In the gastric ulceration which was produced regularly by this method, the lesions

were always multiple and occurred in the glandular (pyloric) part of the stomach. No perforations developed, and no duodenal ulcers were noted. The severity of ulceration was proportional to the dosage of steroid given. Control animals showed many ulcerations of the forestomach but none of the glandular portion.

The mechanism by which steroid action may produce ulceration may include increased volume of gastric secretion, decreased reparative inflammatory reaction of the gastric wall to injury by gastric juice, and decreased secretion of protective mucus by the gastric wall. The steps in the development of forestomach ulceration may consist of (1) the edematous reaction of the gastric wall to injury by concentrated gastric juice in the fasting stomach, (2) compression of vessels by edema, (3) ischemia of the gastric wall, and (4) ulceration. Administration of steroids prevents this type of ulceration by preventing inflammatory edema, but it produces ulceration in the pyloric stomach by the mechanisms already described. The forestomach type of ulceration did not occur in the pyloric stomach, presumably because of the richer vascularity of the pyloric stomach. D. G.

Eosinophilic Response to Intraperitoneal Blood. Chapman, J. S., and Reynolds, R. C.: J. Lab. & Clin. Med. **51**: 516, 1958.

It has been shown that the injection of whole blood into the peritoneum of rats and mice was followed in four to five days by a striking eosinophilic response. This eosinophilic response occurred regardless of whether or not the blood was clotted. The present study was undertaken to determine which components of whole blood were capable of producing the eosinophilic response. White mice were injected intraperitoneally with 1.0 ml. of human heparinized plasma or with washed human red cells resuspended in saline. Smears were obtained from the peritoneum by drawing ordinary glass slides over the surface. These smears were prepared with Wright's stain, and a differential count was done. A striking eosinophilic response followed the injection of human red cells, while only a minimal response occurred following injection of human plasma. The peak of the eosinophilic response to human red cells occurred on the fifth day. Rats were injected intraperitoneally with stroma-free hemoglobin or with hemoglobin-free stroma from their own red cells. Smears from the peritoneum following hemoglobin injection revealed very few cells, all of which were lymphocytes or mononuclears. Smears from the peritoneum following stroma injection revealed a much heavier exudate, rich in eosinophils, the nuclei of which exhibited unusual ring and horseshoe shapes. The granules, however, were typical. It was suggested that the mild eosinophilic response of the mouse peritoneum to injection with human plasma might be associated with the intraperitoneal bleeding from trauma of the injection. Statistical comparison of the reaction of mice to human red cells with the reaction of rats to their own blood indicated that "allergy," as commonly understood, played a minor role in the eosinophilic response of the peritoneum to blood and its components. E. W.

The Effect of Theophylline Ethylenediamine on the Pulmonary Circulation. Storstein, O., Helle, I., and Rokseth, R.: Am. Heart J. **55**: 781, 1958.

Twenty-one patients, including 16 with heart disease and 3 with bronchial asthma, were studied for ventilatory function and subjected to right heart catheterization. Pulmonary artery and PCV pressures were measured, and cardiac output was estimated with a Cournand needle in the femoral

artery. Expired air and blood samples were analyzed for oxygen and carbon dioxide content. Theophylline ethylenediamine (TED) was then administered intravenously and observations were repeated.

Maximal breathing capacity was increased, although there was no change in tidal air or vital capacity. Oxygen saturation was not affected, but arterial pCO_2 diminished. Systemic blood pressure decreased (in one instance markedly) but generally to a lesser degree than pulmonary artery pressure. It is considered that the effect of TED is the dilatation of the bronchi and the arterioles of both pulmonary and systemic circulations. The work of the right ventricle was diminished by TED despite an increase in heart rate. Cardiac output remained unchanged. In hypertensive patients TED administration caused an insignificant amount of pulmonary vasodilatation and an increased cardiac output. E. K.

The Electrocardiogram in Cor Pulmonale Secondary to Pulmonary Emphysema: A Study of 18 Cases Proved by Autopsy. Phillips, R. W.: Am. Heart J. **56**: 352, 1958.

Eighteen patients who died of congestive failure due to cor pulmonale secondary to pulmonary emphysema were autopsied. Electrocardiograms taken over a period of time, and in all cases within one month of death, were analyzed. In about 30 per cent of the cases the ECG and the autopsy showed no evidence of right ventricular hypertrophy. In other cases the ECG indicated and the autopsy disclosed massive right ventricular hypertrophy. In the adult age group studied, the major electromotive force is directed to the left and posteriorly. The second stage of evolution of cor pulmonale is indicated by a shift of electromotive force to the right with maintenance of a posterior orientation. S waves become prominent in the left precordial leads, but R waves are not prominent in the right precordial leads. In the final stage, electric forces are directed to the right and anteriorly, with tall R waves over the right chest leads as well as axis deviation to the right.

None of the patients studied had a history of recurrent attacks of wheezing, suggesting an allergic bronchial asthma. All were heavy cigarette smokers, and 17 evidenced chronic bronchitis; the remaining one had saccular bronchiectasis. E. K.

The Clinical Differentiation of "Allergic" Vasculitis From Periarteritis Nodosa. McCombs, R. P.: Arch. Internat. Allergy & Appl. Immunol. **12**: 98, 1958.

Necrotizing angiitis was recognized pathologically in biopsy or autopsy material of 92 cases. Fifty-eight of these cases were diagnosed clinically as sensitization dermatitis, angioneurotic edema, erythema nodosum, dermatomyositis, thrombocytopenic purpura (due to drug hypersensitivity), temporal arteritis, lupus erythematosus, or periarteritis nodosa. The remaining 34 cases were diagnosed as having "allergic" vasculitis. Pathologic studies in these cases revealed involvement of small arterioles and at times capillaries and veins, but the larger arteries were spared. The clinical data in the cases of "allergic" vasculitis and periarteritis nodosa were compared. "Allergic" vasculitis was a self-limited disease which usually followed drug exposure or an infection. It was manifested by arthralgia, purpura, edema, dermatitis, gastrointestinal bleeding, and moderate to severe renal failure. The author stresses the importance of differentiation of these disorders since spontaneous recovery was common in "allergic" vasculitis and response to corticosteroid therapy was much better than in periarteritis nodosa. The latter disease had a poor prognosis despite all forms of therapy. I. G.

Immunology

Autoantibodies in Human Glomerulonephritis and Nephrotic Syndrome. Liu, C. T., and McCrory, W. W.: J. Immunol. **81**: 492, 1958.

The search for autoantibodies to human kidney tissue in patients with glomerulonephritis or the nephrotic syndrome has yielded conflicting results. The authors used Boyden's hemagglutination (HA) technique in tests on a series of children suffering with these conditions. Human kidney tryptic digest antigens (method of Cole) were employed. They were prepared from tissues obtained post mortem from infants under 2 years of age. The sera of 148 patients were studied. HA titers of 1:20 or higher were found in 71 per cent of 35 cases of acute glomerulonephritis and in 89 per cent of 54 cases of nephrotic syndrome. Among 12 cases with chronic nephritis and 7 with terminal nephrotic syndrome, all but one showed titers of less than 1:20. In 16 normal children the results were negative.

In some patients without renal disease, positive results were obtained. Titers higher than 1:20 were found in 30 per cent of 10 patients with acute rheumatic fever and in 91 per cent of 14 patients with infectious diseases, including measles, viral hepatitis, pneumococcus pneumonia, and others. Four of seven patients with rheumatoid arthritis showed positive HA titers.

The results with lung, liver, and heart tryptic digests were also positive in some of the glomerulonephritis and nephrotic syndrome cases, but the titers for these materials were not as great as for kidney. Ouchterlony gel-precipitation tests performed with sera from glomerulonephritis or nephrotic syndrome patients against whole extracts of human infant kidney, liver, and lung as antigens produced visible precipitin bands to these organs, particularly to kidney and liver. No cross reactions were obtained with organs derived from other species. The visible precipitin bands could not be correlated with the respective antikidney hemagglutinin titers. The antikidney HA test seemed to be species specific but not organ specific or disease specific. B. S.

Antibody Production in Mice Exposed Intermittently to Radium Gamma Rays. Smith, F., Ruth, H. J., and Grenan, M. M.: Proc. Soc. Exper. Biol. & Med. **97**: 451, 1958.

Antibody production and total circulating leukocyte counts were found to be diminished in 5- to 8-week-old male mice following intermittent exposure to radium gamma rays. The total exposure dose to the mice over a 51-day period was about 112 r to one group and 450 r to the others. On the second day after the end of exposure, leukocyte counts were recorded. On the third day the mice were immunized with a single intravenous dose of washed sheep erythrocytes. The animals were sacrificed on the eighth day, and the serum was obtained. Hemolysin titers and leukocytes were diminished by irradiation, more so as irradiation doses increased.

In another experiment, mice that had received a "chronic" accumulation of 450 r of radium gamma rays were subjected, four days later, to 150 r, 250 r, or 350 r of x-rays. Immunization was done one week after this acute exposure. No evidence was found that the prior irradiation exposure altered radiation sensitivity to either antibody production or the hematopoietic process. Total circulating leukocyte counts were somewhat lower for mice given the additional acute exposure, and the counts decreased as the acute exposures increased.

The possibility that hematopoiesis and antibody production may be independent processes during recovery from irradiation is discussed.

H. Stryker.

An Effect of Antigen-Antibody Interaction on Blood Coagulation. Robbins, J., and Stetson, C. A., Jr.: J. Exper. Med. **109**: 1, 1959.

Rabbits immunized to bovine serum albumin, bovine gamma globulin, or ovalbumin were bled. Clotting, when measured in siliconized tubes, took place in from 20 to 40 minutes normally. The addition of specific antigen to the blood of sensitized animals induced much more rapid coagulation, the effect being proportional to the amount of antigen added. Clotting time was unaffected in controls when antigen was added. Mixtures of antigen and serum from immunized rabbits were added in vitro to blood from normal rabbits; again coagulation was accelerated. This effect was observed over a wide range of dilutions of antigen and antiserum. Natural antigens, such as the somatic antigen of *E. coli* and the polysaccharide, dextran, exhibited a similar effect in accelerating clotting. This effect was further enhanced by the immunization of rabbits to *E. coli,* suggesting that the acceleration of clotting was due to an antigenic reaction rather than an endotoxic property of this bacterial antigen. The removal of rabbit platelets from the testing system before the addition of dextran or *E. coli* endotoxin prevented the acceleration of clotting. It is suggested that the effect of antigen-antibody reaction on the clotting mechanism is a general one found in each of several antigen systems and may be mediated by an effect on the platelets. E. K.

Antistaphylolysin Determinations in the Sera of Children With Bronchial Asthma. Harnaes, K. R., and Borgen, P. H. F.: Acta allergol. **12**: 336, 1958.

The antistaphylolysin titers in the sera of 113 asthmatic children from 1 to 13 years of age were measured and compared with a control group of 58 children of similar ages. Significantly, more asthmatic children had elevated antistaphylolysin titers, using a titer of 2 as an abnormally elevated value. In the asthmatic group there was no significant difference in elevated titers among skin-test-positive and skin-test-negative patients. There was a tendency toward higher titer values in the skin-test-negative group. M. C.

Miscellaneous

Circulating Eosinophils in Labor and Puerperium. Marcus, M. B., Cibley, L. J., Brandt, M. L., Millman, L., and Barlas, D.: Am. J. Obst. & Gynec. **75**: 11, 1958.

One-hundred twenty-four women were examined for circulating eosinophils in early labor and on two occasions in the early puerperium. Average eosinophil counts in early labor were 80 to 86 cubic millimeters. On the third to the fifth post-partum day an increase was noted, "the average count varying from 425 to 600 per cubic millimeter." In 9 patients who developed complications of labor, continuance of the eosinopenic state was found. E. K.

Chlorpheniramine Maleate in Prophylaxis of Pyrexial Reactions During Blood Transfusions. Hobsley, M.: Lancet **1**: 497, 1958.

The use of antihistamines in preventing blood transfusion reactions was evaluated by the addition of 10 mg. of chlorpheniramine maleate (Chlor-Trimeton) to every other bottle of blood in 200 consecutive cases. Pyrogenic reactions were assessed by taking oral temperatures, starting one half-hour before the transfusion and continuing each half-hour for 2 hours after the completion of the transfusion. Alternate patients were placed in the control

group except where multiple transfusions were given the same patients, in which case they were assigned alternately to each group. Patients were carefully queried regarding symptoms during the transfusion, especially as to whether they experienced any side effects from the chlorpheniramine. Fifty-seven multiple transfusions were given to the controls, and 55 repeat transfusions were given to patients in the study group. Mild drowsiness which occurred in 3 patients was the only side effect observed from chlorpheniramine. The over-all incidence of pyrogenic transfusion reactions was 35 per cent. No evidence was obtained that would indicate that the antihistamine was effective in preventing the pyrogenic reaction. Laboratory tests ruled out hemolysis due to blood group incompatibility as a cause of pyrexia, and an excessive incidence of pyrogens in the transfusion apparatus was also ruled out since this type of response was not observed when the same apparatus was used with just electrolyte infusions during subsequent months. The author assumes that the higher incidence of pyrexia (35 per cent) observed in his series as compared to the normal of 5 per cent is due to the fact that patients are not usually closely observed for temperature changes following transfusions. The use of antihistamines in transfusions, however, is still recommended for patients with a known history of previous allergic disease. R. W.

The Treatment of Major Allergic Manifestations With Dimetane Injectable. Thomas, J. W.: Ann. Allergy **17**: 25, 1959.

Dimetane injectable gave excellent relief to 23 of 25 patients suffering from various allergic diseases. The medication, administered by the intravenous, intramuscular, or subcutaneous routes, was notably effective in alleviating pain and itching, particularly in patients suffering from the arthralgia and urticaria types of drug reaction. The only side effect noted was some drowsiness, and this occurred in only 3 of the 25 patients comprising the series. H. F.